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09/724,425	11/28/2000	John C. Reed	10412-026	7441

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EXAMINER	
SCHMIDT, MARY M	

ART UNIT	PAPER NUMBER
1635	19

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/724,425	REED, JOHN C.	
	Examiner	Art Unit	
	Mary M. Schmidt	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *27-51* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27-51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 27-51 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 27 is drawn to a method of treating cancer in a human comprising administering an amount of anticode oligomer effective for treating said cancer, wherein said anticode oligomer is from 10 to 40 bases in length and hybridizes to a translation initiation sequence of SEQ ID NO:19. Claim 28 states the method of claim 27, wherein said translation initiation sequence is ATG. Claim 29 states the method of claim 27, further comprising administering one or more chemotherapeutic agents.

Claim 30 is drawn to a method of treating cancer in a human comprising administering an amount of anticodeoligomer effective for treating said cancer, wherein said anticode oligomer is from 10 to 40 bases in length and hybridizes to a splice donor sequence of SEQ ID NO:19. Claim 31 states the method of claim 30, wherein said splice donor sequence is GT. Claim 32

states the method of claim 30, further comprising administering one or more chemotherapeutic agents.

Claim 33 is drawn to a method of treating cancer in a human comprising administering an amount of anticode oligomer effective for treating said cancer, wherein said anticode oligomer is from 10 to 40 bases in length and hybridizes to a splice acceptor sequence of SEQ ID NO:19. Claim 34 states the method of claim 33, wherein said splice acceptor sequence is AG. Claim 35 states the method of claim 33, further comprising administering one or more chemotherapeutic agents.

Claim 36 is drawn to a method of treating cancer in a human comprising administering an amount of anticode effective for treating said cancer, wherein said anticode oligomer is from 10 to 40 bases in length and hybridizes to at least one codon of the first six codons of the open reading frame of SEQ ID NO:19. Claim 37 states the method of claim 36, further comprising administering one or more chemotherapeutic agents.

Claim 38 is drawn to a method of treating cancer in a human comprising administering an amount of anticode oligomer effective for treating said cancer, wherein said anticode oligomer is from 10 to 40 bases in length and hybridizes to the 5' cap region of SEQ ID NO:19. Claim 39 states the method of claim 38 further comprising administering one or more chemotherapeutic agents. Claim 40 states the method as in any one of claims 29, 32, 35, 37 and 39 wherein the administration of said anticode oligomer and said one or more chemotherapeutic agents increases the sensitivity of said disorder or cancer to said one or more chemotherapeutic agents. Claim 41

states the method as in any one of claims 27, 30, 33, 36 and 38, wherein said cancer is non-Hodgkin's lymphoma, prostate cancer, breast cancer, gastro-intestinal cancer or colon cancer.

Claim 42 is drawn to a pharmaceutical composition comprising an anticode oligomer, wherein said anticode oligomer is from 10 to 40 bases in length and hybridizes to a translation initiation sequence of SEQ ID NO:19, and a pharmaceutically acceptable carrier. Claim 43 is drawn to a pharmaceutical composition an anticode oligomer, wherein said anticode oligomer is from 10 to 40 bases in length and hybridizes to a splice donor sequence of SEQ ID NO:19, and pharmaceutically acceptable carrier. Claim 44 is drawn to a pharmaceutical composition comprising an anticode oligomer, wherein said anticode oligomer is from 10 to 40 bases in length and hybridizes to a splice acceptor sequence of SEQ ID NO:19, and a pharmaceutically acceptable carrier. Claim 45 is drawn to a pharmaceutical composition comprising an anticode oligomer, wherein said anticode oligomer is from 10 to 40 bases in length and hybridizes to at least one codon of the first six codons of the open reading frame of SEQ ID NO:19, and a pharmaceutical carrier. Claim 46 is drawn to a pharmaceutical composition comprising an anticode oligomer, wherein said anticode oligomer is from 10 to 40 bases in length and hybridizes to the 5' cap region of SEQ ID NO: 19, and a pharmaceutically acceptable carrier.

Claims 47 through 51 are drawn to a method for increasing the sensitivity of a tumor cell to a chemotherapeutic agent, comprising exposing said cell to the pharmaceutical composition of claims 42 through 46.

MPEP 2163 teaches the following conditions for the analysis of the claimed invention at the time the invention was made in view of the teachings of the specification and level of skill in the art at the time the invention was made:

> The claimed invention as a whole may not be adequately described where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence....A lack of written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process....Generally, there is an inverse correlation between the level of skill and knowledge in the art and the specificity of disclosure necessary to satisfy the written description requirement....The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice..., reduction to drawings..., or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.

The claims lack written description since the claims are drawn to methods of treatment of a human and pharmaceutical compounds having the functional use for treatment, which require a knowledge of the described disease states which are treated upon administration of the claimed compounds. In the instant case, the claimed disease states are different types of cancer (note claim 27 is broadly drawn to treatment of any type of cancer for instance) and the whole organism treated is a human. The invention thus rests on the correlation of a desired treatment function to the claimed and disclosed therapeutic compounds. The specification as filed,

however, does not teach any specific identifying design characteristics of any bcl-2 antisense oligonucleotide to instant SEQ ID NO:19 having a clear inhibition of the bcl-2 gene in a human such that the function of treating, stabilizing, or preventing cancer is achieved *in vivo*. The post art supplied by Applicant (Webb et al. and Waters et al.) provides a correlation between instant SEQ ID NO:17 (the Genta antisense to the first 6 codons of the coding region of instant SEQ ID NO:19) and treatment of cancer in a whole organism, however, this sequence is not considered to be a representative number of species of any antisense of 10 to 40 bases directed to instant SEQ ID NO:19, nor to any of the claimed regions of instant SEQ ID NO:19. In the absence of a more specific description of the design criteria (ie., specific sequences, modifications, routes of administration, formulation) needed to visualize bcl-2 antisense effective for treatment of any cancer as claimed, one of skill in the art would not have sufficient written description of the claimed compounds. Therefore, the specification as filed does not show that Applicants' were in possession of (the knowledge of) a representative number of anti-bcl-2 antisense compounds at the time the invention was made to teach possession of the invention having the claimed functional limitations for treatment of cancer in humans.

Claims 43-44 and 46 further lack written description for a representative number of species of the claimed antisense to splice donor, splice acceptor and cap region of SEQ ID NO:19. The specification as filed only teaches on page 13 the sequence of one splice acceptor and splice donor region. The specification as filed thus does not provide an adequate description of other possible splice acceptor and donor regions, nor cap regions as filed. Absent further

specific guidance as to other regions considered splice acceptor, donor and cap regions, one of skill in the art would not have recognized that applicant was in possession of the breath of antisense claimed to any such region.

The claims further lack written description for the breath of any oligomer that "hybridizes" to the claimed target regions. The specification as filed does not define any particular metes and bounds for the breath of conditions claimed that are embraced by the use of the word "hybridizes". Since the claims are drawn to methods of treatment of cancer and pharmaceutical compositions having implied therapeutic use, one of skill in the art would not have recognized that applicant was in possession of a representative number of species of any possible nucleic acid that hybridizes to the claimed regions absent further description of the hybridization conditions such as stringency and salt concentration. As it stands, the claims read on any nucleic acid in which at least one base is capable of hybridizing to the target region. Thus, the claims as written lack written description of the breath of oligomers claimed since the specification as filed does not clearly define a representative number of species of any such antisense that could potentially hybridize in some capacity to the claimed bcl-2 target gene regions.

3. Claims 27-51 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of administration to a human for treatment of cancer comprising, and pharmaceutical compositions comprising, the anticode oligomer to the first six

codons of the coding region of SEQ ID NO:19 (instant SEQ ID NO:17, the antisense known as G3139 in the post-art (Webb et al. and Waters et al.) and having the sequence of 5'-TCTCCCAGCGTGCGCCAT-3'), does not reasonably provide enablement for administration of any antisense to instant SEQ ID NO:19, or pharmaceutical compositions thereof, as claimed for the breath of target regions claimed for administration to a whole organism subject (*in vivo*) for the therapeutic functions claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claim 27 is drawn to a method of treating cancer in a human comprising administering an amount of anticode oligomer effective for treating said cancer, wherein said anticode oligomer is from 10 to 40 bases in length and hybridizes to a translation initiation sequence of SEQ ID NO:19. Claim 28 states the method of claim 27, wherein said translation initiation sequence is ATG. Claim 29 states the method of claim 27, further comprising administering one or more chemotherapeutic agents.

Claim 30 is drawn to a method of treating cancer in a human comprising administering an amount of anticodeoligomer effective for treating said cancer, wherein said anticode oligomer is from 10 to 40 bases in length and hybridizes to a splice donor sequence of SEQ ID NO:19. Claim 31 states the method of claim 30, wherein said splice donor sequence is GT. Claim 32 states the method of claim 30, further comprising administering one or more chemotherapeutic agents.

Claim 33 is drawn to a method of treating cancer in a human comprising administering an amount of anticode oligomer effective for treating said cancer, wherein said anticode oligomer is from 10 to 40 bases in length and hybridizes to a splice acceptor sequence of SEQ ID NO:19. Claim 34 states the method of claim 33, wherein said splice acceptor sequence is AG. Claim 35 states the method of claim 33, further comprising administering one or more chemotherapeutic agents.

Claim 36 is drawn to a method of treating cancer in a human comprising administering an amount of anticode effective for treating said cancer, wherein said anticode oligomer is from 10 to 40 bases in length and hybridizes to at least one codon of the first six codons of the open reading frame of SEQ ID NO:19. Claim 37 states the method of claim 36, further comprising administering one or more chemotherapeutic agents.

Claim 38 is drawn to a method of treating cancer in a human comprising administering an amount of anticode oligomer effective for treating said cancer, wherein said anticode oligomer is from 10 to 40 bases in length and hybridizes to the 5' cap region of SEQ ID NO:19. Claim 39 states the method of claim 38 further comprising administering one or more chemotherapeutic agents. Claim 40 states the method as in any one of claims 29, 32, 35, 37 and 39 wherein the administration of said anticode oligomer and said one or more chemotherapeutic agents increases the sensitivity of said disorder or cancer to said one or more chemotherapeutic agents. Claim 41 states the method as in any one of claims 27, 30, 33, 36 and 38, wherein said cancer is non-Hodgkin's lymphoma, prostate cancer, breast cancer, gastro-intestinal cancer or colon cancer.

Claim 42 is drawn to a pharmaceutical composition comprising an anticode oligomer, wherein said anticode oligomer is from 10 to 40 bases in length and hybridizes to a translation initiation sequence of SEQ ID NO:19, and a pharmaceutically acceptable carrier. Claim 43 is drawn to a pharmaceutical composition an anticode oligomer, wherein said anticode oligomer is from 10 to 40 bases in length and hybridizes to a splice donor sequence of SEQ ID NO:19, and pharmaceutically acceptable carrier. Claim 44 is drawn to a pharmaceutical composition comprising an anticode oligomer, wherein said anticode oligomer is from 10 to 40 bases in length and hybridizes to a splice acceptor sequence of SEQ ID NO:19, and a pharmaceutically acceptable carrier. Claim 45 is drawn to a pharmaceutical composition comprising an anticode oligomer, wherein said anticode oligomer is from 10 to 40 bases in length and hybridizes to at least one codon of the first six codons of the open reading frame of SEQ ID NO:19, and a pharmaceutical carrier. Claim 46 is drawn to a pharmaceutical composition comprising an anticode oligomer, wherein said anticode oligomer is from 10 to 40 bases in length and hybridizes to the 5' cap region of SEQ ID NO: 19, and a pharmaceutically acceptable carrier.

Claims 47 through 51 are drawn to a method for increasing the sensitivity of a tumor cell to a chemotherapeutic agent, comprising exposing said cell to the pharmaceutical composition of claims 42 through 46.

Please note that claims 42-46 would be free of the instant rejection if the word "pharmaceutical" was removed from the preamble.

The specification as filed teaches design of antisense on page 13, Table 1, to the translation initiation region, splice donor region and splice acceptor region of instant SEQ ID NO:19, and teaches on page 44 the sequence of instant SEQ ID NO:17 to the first six codons of human bcl-2 open reading frame (instant SEQ ID NO:19). The specification as filed only teaches administration of these antisense to cells in cell culture and does not teach any further administration of these any antisense to human bcl-2 (instant SEQ ID NO:19) to a whole organism for the therapeutic functions claimed.

However, as pointed out by Applicant, the post-art teaches the therapeutic use of instant SEQ ID NO:17, the antisense to the first 6 codons of the open reading frame of instant SEQ ID NO:19 as having use in treatment of humans for cancer. Thus, the claims are considered enabled for the breath of methods and pharmaceutical compositions claimed which embrace use of this specific antisense oligonucleotide. The claims are not considered further enabled for the breath of any other antisense oligonucleotide for the claimed methods and pharmaceutical compositions having implied therapeutic use because of the high level of unpredictability in the prior and post art for design of antisense oligonucleotides having *in vivo* uses. There is no guidance in the specification as filed for the specific design of antisense to human bcl-2 (instant SEQ ID NO:19) having *in vivo* functions for the claimed treatments of cancer, and the post-art teaching of success of instant SEQ ID NO:19 does not provide further guidance for making and using any other antisense to instant SEQ ID NO:19 for the functions of *in vivo* use since the high

level of unpredictability in the art requires an analysis of each independent antisense for *in vivo* treatment uses.

There is a high level of unpredictability known in the antisense art for therapeutic, *in vivo* (whole organism) applications. The factors considered barriers to successful delivery of antisense delivery to the organism are: (1) penetration of the plasma membrane of the target cells to reach the target site in the cytoplasm or nucleus, (2) withstanding enzymatic degradation, and (3) the ability to find and bind the target site and simultaneously avoid non-specific binding (see Branch). Note also Ma et al. who teach (on page 167) that "to gain therapeutic advantage using antisense-based technology, ODNs must have certain characteristics. They must be resistant to degradation, internalize efficiently, hybridize in a sequence specific manner with the target nucleic acid, display adequate bioavailability with a favorable pharmacokinetic profile and be nontoxic." Despite the synthesis of more resilient, nuclease resistant, oligonucleotide backbones and isolated successes with antisense therapy *in vivo*, the majority of designed antisense molecules still face the challenge of successful entry and localization to the intended target and further such that antisense and other effects can routinely be obtained. Flanagan teaches, "oligonucleotides (*in vivo*) are not distributed and internalized equally among organs and tissues.... Unfortunantly, therapeutically important sites such as solid tumors contain very little oligonucleotide following intravenous injections in animals (page 51, column 2)." Ma et al. supports the difficulties of *in vivo* use of ODNs on pages 160-172. Jen et al. further taught that "given the state of the art, it is perhaps not surprising that effective and efficient clinical

translation of the antisense strategy has proven elusive. While a number of phase I/II trials employing ONs have been reported..., virtually all have been characterized by a lack of toxicity but only modest clinical effects." (Page 315, col. 2) Green et al. summarizes that "the future of nucleic acid therapeutics using antisense ODNs ultimately depends on overcoming the problems of potency, stability, and toxicity; the complexity of these tasks should now be apparent. Improvements in delivery systems and chemical modifications may lead to safer and more efficacious antisense compounds with improved pharmacokinetics and reduced toxicities." (P. 103, col. B) Note also some of the major outstanding questions that remain in the art taught by Agrawal et al. On page 79, col. 2.

In vitro, antisense specificity to its target may be manipulated by "raising the temperature or changing the ionic strength, manipulations that are commonly used to reduce background binding in nucleic acid hybridization experiments." (Branch, p. 48) Note also Ma et al. who teach that "*in vitro* subcellular distribution is dependent on the type of ODN modification, cellular system and experimental conditions. ODNs, once internalized, are distributed to a variety of subcellular compartments." (Page 168) Discovery of antisense molecules with "enhanced specificity" *in vivo* requires further experimentation for which no guidance is taught in the specification. Note Branch who teaches the state of the art for designing an antisense which inhibits a target *in vivo:* it "is very difficult to predict what portions of an RNA molecule will be accessible *in vivo*, effective antisense molecules must be found empirically by screening a large number of candidates for their ability to act inside cells (Branch, p.49)." Note Jen et al. who

teach that "although mRNA targeting is impeccable in theory, many additional considerations must be taken into account in applying these strategies in living cells including mRNA site selection, drug delivery and intracellular localization of the antisense agent." (Abstract) Bennett et al. further taught that "although the antisense paradigm holds great promise, the field is still in its early stages, and there are a number of key questions that need to be answered and technical hurdles that must be overcome....The key issues concerning this class of chemicals center on whether these compounds have acceptable properties as drugs. These include pharmacokinetic, pharmacological and toxicological properties." (Page 13) As argued above, these issues remain unpredictable in the art for antisense oligonucleotide administration *in vivo*.

One of skill in the art would not accept on its face the successful delivery of the disclosed antisense molecules *in vivo* and further, treatment effects, in view of the lack of guidance in the specification and the unpredictability in the art. Neither the specification nor technology today teach general guidelines for successful delivery or treatment effects of antisense molecules in whole organisms. Specifically the specification does not teach (1) stability of the antisense molecule *in vivo*, (2)effective delivery to the whole organism and specificity to the target tissues, (3) dosage and toxicity, nor (4) entry of molecule into cell and effective action therein marked by visualization of the desired treatment effects. These key factors are those found to be highly unpredictable in the art as discussed *supra*. The lack of guidance in the specification as filed for these factors would therefore require "trial and error" experimentation beyond which is taught by

the specification as filed. Therefore, it would require undue experimentation to practice the invention as claimed.

The claims are further not enabled for the breath of any antisense that hybridizes to the claimed bcl-2 gene target regions since the specification as filed does not teach the conditions such as stringency, salt concentration, etc. under which any such oligomer may hybridize to the target for the claimed functions of treatment of cancer. Similarly, the pharmaceutical compositions are not enabled for the breath of any antisense that could possibly hybridize to some extent to the claimed bcl-2 gene target regions since the oligomers of those claims have implied therapeutic use. As stated above, there is a high level of unpredictability in the field of antisense development for use in treatment of a whole organism. In view of this unpredictability, one of skill in the art would necessarily practice an undue amount of experimentation to make and use the breath of antisense claimed since neither the specification as filed nor the prior art taught the hybridization conditions needed to use any antisense of 10-40 bases to the claimed regions of instant SEQ ID NO:19 for the claimed uses in a whole organism.

Response to Arguments

4. Applicant's arguments filed 3/10/03 have been fully considered but they are not persuasive.

Applicant states that "Examples 2-18 of the specification provide data from both in vitro and cell based assays which demonstrate the efficacy of the claimed oligonucleotides in reducing

the level of bcl-2 and in killing cancer cells, in particular lymphoma cells (pp. 21-57 of the specification). The data generated from the cell based assays demonstrates the ability of the antisense oligomers of the invention to permeate across the membrane of eukaryotic cells, hybridize to the bcl-2 mRNA in its native form and effectively inhibit the growth of a variety of tumor cells. The specific "antisense effect" of the antisense oligomers is confirmed by the complete inability of the control sense oligomers to affect cell growth. Further, the efficacy of the claimed invention as demonstrated in cell based assays has been confirmed by the post-filing art. Ij particular, it has been shown that the pharmaceutical compounds and methods of the instant invention reduced tumor mass and led to an improvement in symptoms for cancer patients. (Webb et al., 1997, Lancet 349:1137-41)."

As stated in the rejection above, the data taught by Webb et al. has been considered to enable the breath of the instant invention drawn to use of the sequence of instant SEQ ID NO:17, the first six codons to the open reading frame of instant SEQ ID NO:19. However, for the reasons stated above, any other antisense taught in the instant specification or which bind to instant SEQ ID NO:19 are not considered enabled for the breath of claimed use in a human for treatment due to the high level of unpredictability in making and using antisense to a whole organism. As demonstrated above, the results found in cells in cell culture (*in vitro*) do not necessarily correlate to use of such antisense for treatment in a human due to the complexity of the *in vivo* environment (see the unpredictable factors argued above).

Applicant further states that "[m]oreover, Delihas has described numerous clinical trials that are underway on various types of cancer using the compositions and methods of the instant invention. (Delihas, 2001...). These studies confirm that the antisense oligomers of the invention can be used to treat cancer patients when used in accordance with the teaching of the specification. These studies further confirm that one skilled in the art would be able to follow the teaching of the specification and use the cell based data proved therein to treat cancer patients with the claimed oligomers without undue experimentation. In order to satisfy the enablement requirement, a considerable amount of experimentation is permissible and not considered undue, so long as it is merely routine.... Applicant reasserts that the claimed invention is fully enabled, and should not be precluded by the necessity for some experimentation involving routine screening and testing...."

The teachings of Delihas et al. also show use of the ASO G3139 (Genta, Inc.), which is the same sequence as instant SEQ ID NO:17. Thus, the teachings of Delihas et al. also support the enabled breath of the instant invention, but do not further provide other antisense to human bcl-2, instant SEQ ID NO:19, nor guidance for the design of other antisense to instant SEQ ID NO:19 showing that the breath of the instant claims was enabled at the time the invention was made. Contrary to applicants assertions, more than routine screening is necessary to identify and antisense that is functional for therapeutic purposes in a human. As cited above, the ability to locate an accessible binding region even for demonstrated gene inhibition in cells in cell culture is not sufficient to overcome the unpredictable factors for use in cells in a human. Thus, the

teachings of Delihas et al. and the other cited references, Webb et al. and Waters et al., showing use of instant SEQ ID NO:17, does not correlate to the ability of one of skill in the art to make and use antisense to other regions of instant SEQ ID NO:19, absent *de novo* trial and error experimentation to find antisense with the claimed therapeutic functions *in vivo*, the amount of which is considered undue.

Applicant further states that the expectation of success for identifying a useful bcl-2 antisense oligonucleotides of 10 to 40 bases in length targeted against the strategic sites of SEQ ID NO:19 is no less than testing an array of hundreds (or thousands) of hybridomas to identify one useful monoclonal antibody, and thus the claimed invention is clearly within the purview o the skilled artisan."

However, the experimentation to practice the instant invention is not based on identification of antibodies, but rather on use of antisense to bcl-2, which when administered to a human (ie. not the subject of a mass screening project), will have the claimed functions, treatment of cancer. There is thus no comparison between identification of antibodies and antisense having specific therapeutic functions in a human.

Applicant further states that "the instant specification provides objective scientific data demonstrating antisense activity that reasonably *correlates* to *in vivo* applications. In fact, such assays are routinely used in the art of antisense technology to identify and test antisense oligonucleotides for human treatment."

However, the references cited above contradict applicants' assertion of the routine nature of identification of antisense having therapeutic properties in *in vivo* applications since there is not general guidance in the art for design of antisense having specific therapeutic functions. Each desired function is unique due to the complexity of disease states. For treatments dependent on down-regulation of a specific gene, the scenario for which use of antisense is an attractive approach, must be considered with specific antisense oligonucleotides for the ability to actually use certain antisense *in vivo* for the claimed functions. The references cited above teach that while it is routine for *in vitro* screening, there is no correlation to an expectation that an antisense which binds a gene target in cells in cell culture will function to bind and treat a disease in a whole organism. Gene target sites may be accessible to antisense in cells in cell culture, but are not readily accessible to antisense *in vivo* due to the complexity of the whole organism environment. Thus, each antisense must be considered on a case by case basis.

5. The prior art does not teach nor fairly suggest design and administration of antisense to human bcl-2 (instant SEQ ID NO:19) for treatment of whole organisms as instantly claimed, nor pharmaceutical compositions of the claimed antisense to human bcl-2 (instant SEQ ID NO:19) having the claimed *in vivo* uses and to the claimed regions.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to *Mary M. Schmidt*, whose telephone number is (703) 308-4471.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *John LeGuyader*, may be reached at (703) 308-0447.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group Analyst, *Katrina Turner*, whose telephone number is (703) 305-3413.

M. M. Schmidt
June 16, 2003

JOHN L. LeGUYADER
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600